癌症及化學治療

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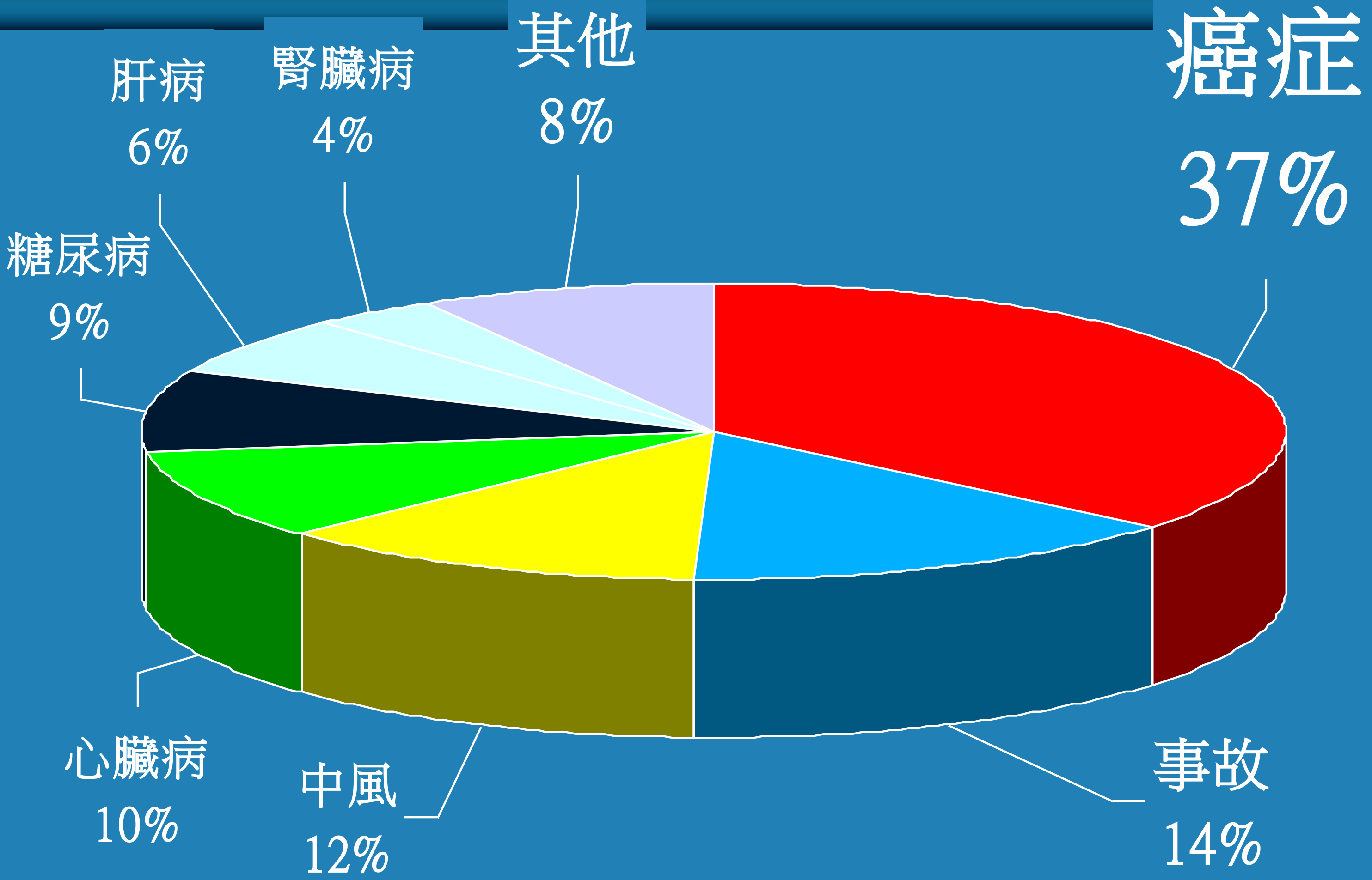
Outline

- Cancer Problems
- Theory of Chemotherapy
- Chemotherapy Agents
- Administering Chemotherapy

Cancer Problems

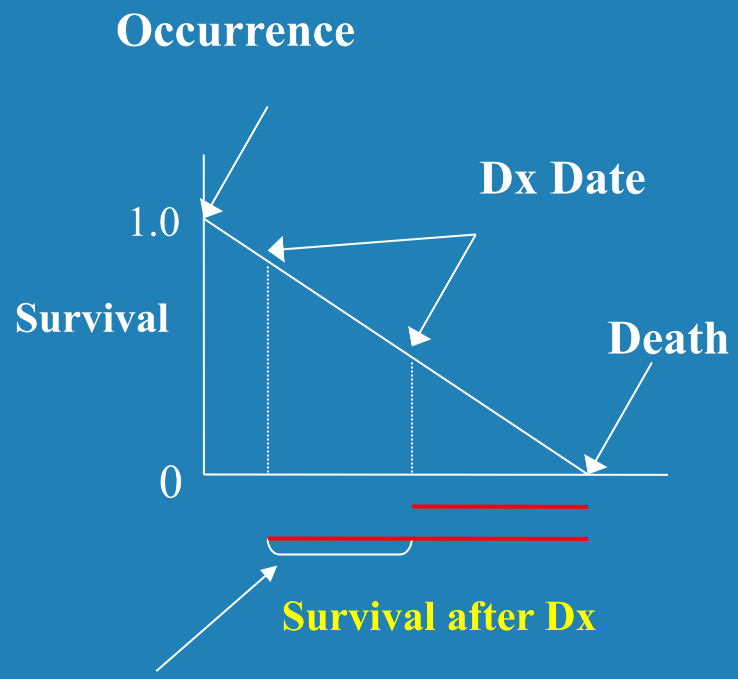
國人死亡原因



Picture of Cancer

- 發生率：增加中﹝esp. 肺、攝護腺、皮膚﹞
- 存活率：增加 5Y survival﹝10% in 1960s → 50% in 2000s﹞
  - Lead-time bias (early detection → prolong survival).
  - Improved treatment : OP, R/T, C/T (L/L, testis, lung…), Target therapy.
  - Improved supportive care.

Early Diagnosis & Lead Time Bias



Lead time bias: increased survival time due to earlier diagnosis.

Cancer Chemotherapy

Introduction

Cancer Treatment Modalities

- Surgery
  - 麻醉術：local, debulking
- Radiation
  - 放射線：local, log-kill
- Chemotherapy
  - 芥子氣：systemic, log-kill
- Molecular targeted therapy
  - 分生學：systemic, highly selective

化學治療

- 物理治療 VS 化學治療
- 廣義化學治療：用化學藥物來治療
- 癌症化學治療？ 感染化學治療？
- **Chemotherapy** **Antibiotics**

Chemotherapy	Antibiotics
Cancer cell	Bact, fung, virus
Cytotoxic	Non-cytotoxic
Non-specific	Specific

癌細胞生長速度

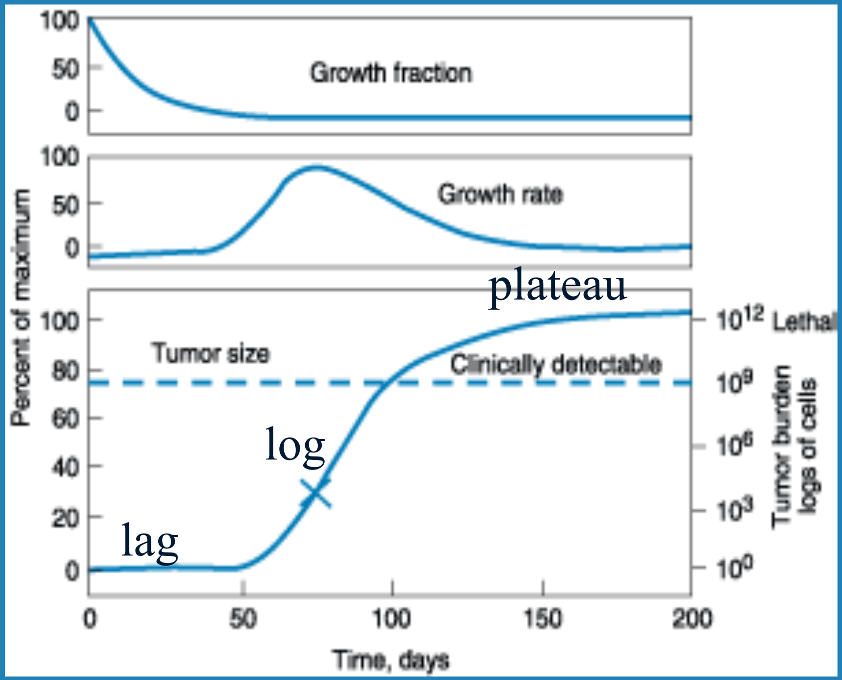
- 一毫克：10^6 cells
- 一公克：10^9 cells
- 一公斤：10^{12} cells
- 致死量：10^{12}-10^{13}

- **Gompertzian Growth**

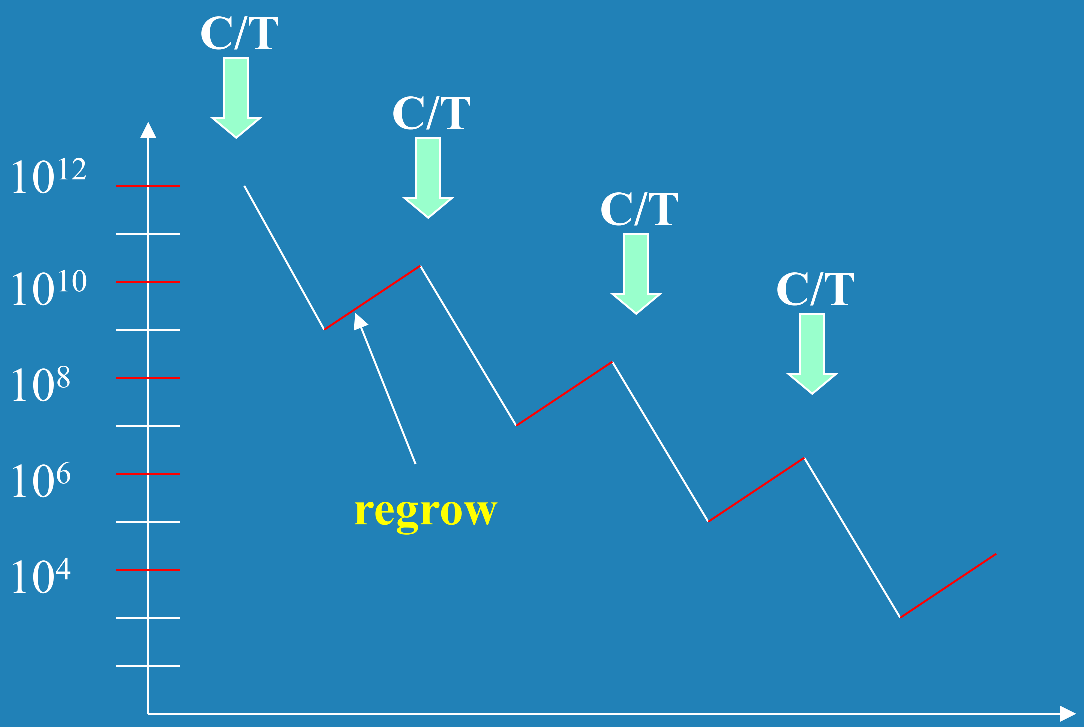
  Growth fraction ↘

  Growth rate ↘

  -- when tumor size ↗



Theory of Log-kill (fractional kill)



Problems in Log-kill

- Drug toxicity & pt compliance – limits dose-intensity.
- Drug accessibility – influenced by blood supply, fibrosis.
  - Bulky tumor, tumor necrosis, few vessels
- C/T sensitivity – not homogenous & may change during treatment
  - Increasing G0, refractory cells

Toxicity & Compliance

- Efficacy vs toxicity
  - MTD (maximally tolerated dose) – dose-limiting toxicity
- Pretreatment evaluation
  - Performance status, age
  - Major organ function
    - Liver, Renal, heart, lung, marrow
  - previous toxicity, infection…
- Prevent toxicity
  - Vomiting, leukopenia …

Escape from the Log-kill

Kinetic Resistance

- Scheduling
  - prevent escape of cancer cells
  - synchronize cells for phase-killing
- Recruiting resting (G0) cells
  - Debulking surgery or R/T
    - Gompertian principle
  - Add cycle-nonspecific agent

Biochemical Resistance

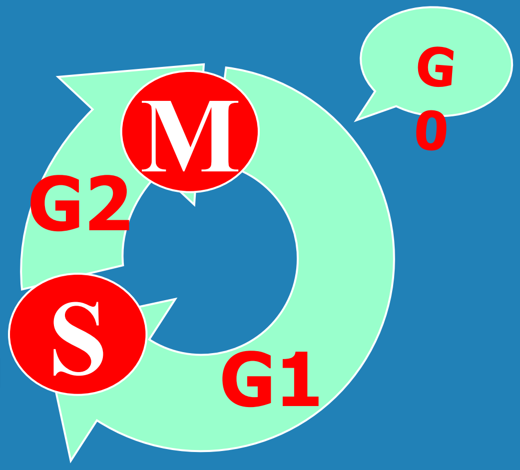
- Combating MDR
  - MDR → drug efflux pump → low concentration in cancer cell
  - P-glycoprotein, MDR protein, lung resistance protein …
    - Ca blocker, CSP (PSC-833)…
- Rescue AE → high-dose C/T
  - Leucovorin, GF (G-, GM-, IL11)
  - Stem cell transplantation

化學治療：Classification

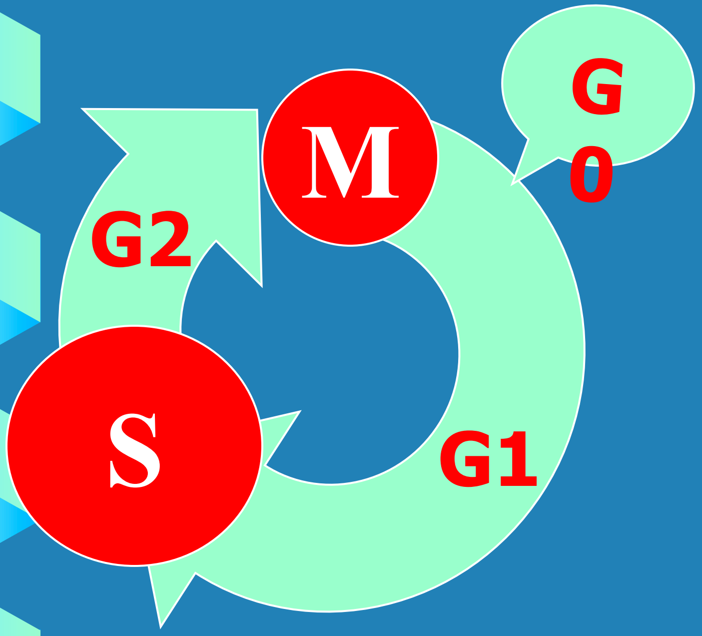
- Alkylating agents
- Antibiotics
- Anti-metabolites
- Mitotic inhibitor
- Topoisomerase inhibitor
- Other

Cell Cycles & C/T

- Marked variation – 16h to 260h.
  - Tumor doubling time ~ 30-300d.
- Cycle-nonspecific:
  - effect all, even resting cells (G0).
  - Nitrosourea
- Cycle-specific:
  - effect except G0.
  - Alkylator, A/B, Platinum



Cell Cycle & Chemotherapy



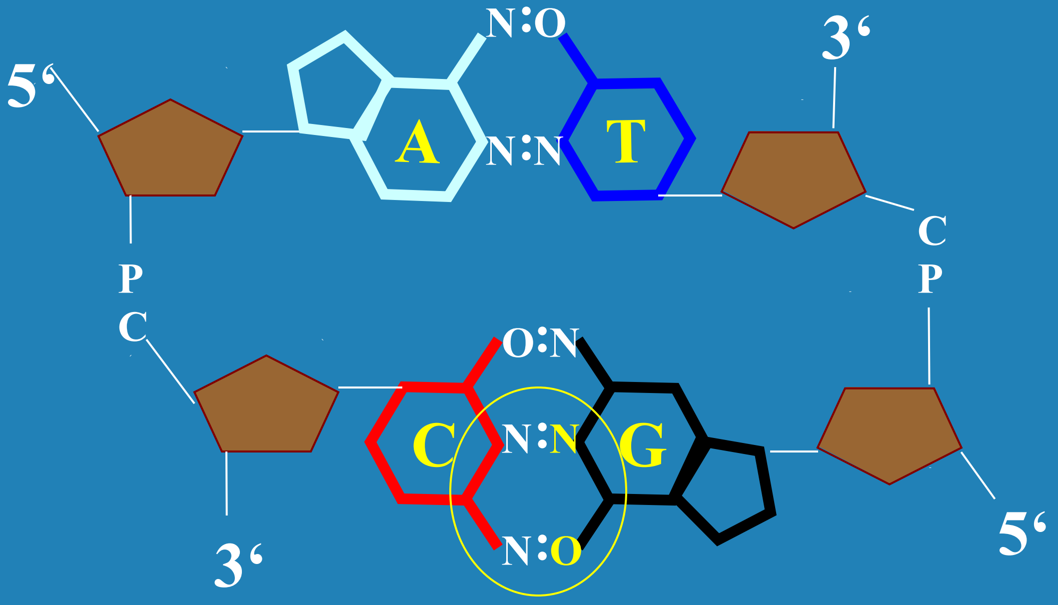
Cycle & phase-specific

	Synthesis	Drug
G1	Protein (enz, 結構)	Asparaginase, Steroid
S	DNA, histone	Antimetabolite Topo I inhibitor
G2	Mitosis regulator	BLM, Taxol, Topo II inh.
M	Mitosis apparatus	Vinca, Navelbine.

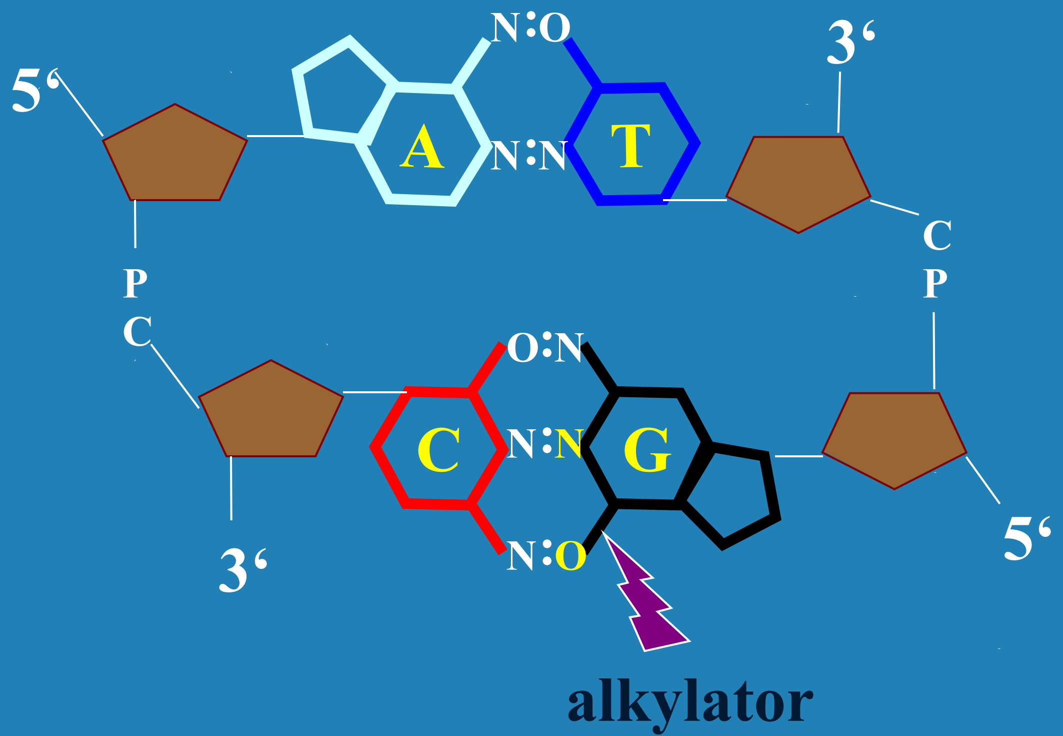
Alkylating Agent

- 機制：**Alkyl** 結合**-NH-, -CO-, -S-, -PO- (esp. guanine**之 **N^7, O^6)**，破壞**DNA**；**cycle-specific**
- **Mustard:**
  - **Nitrogen mustard, chlorambucil, cyclophosphamide, estramustine, ifosfamide, melphalan, busulfan, thiotepa**
- **Triazene: Dacarbazine, procarbazine, temozolamide**
- **Nitrosoureas: BCNU, CCNU, streptozocin**
- **Metal: Cisplatin, carboplatin, oxaliplatin**

DNA Helix



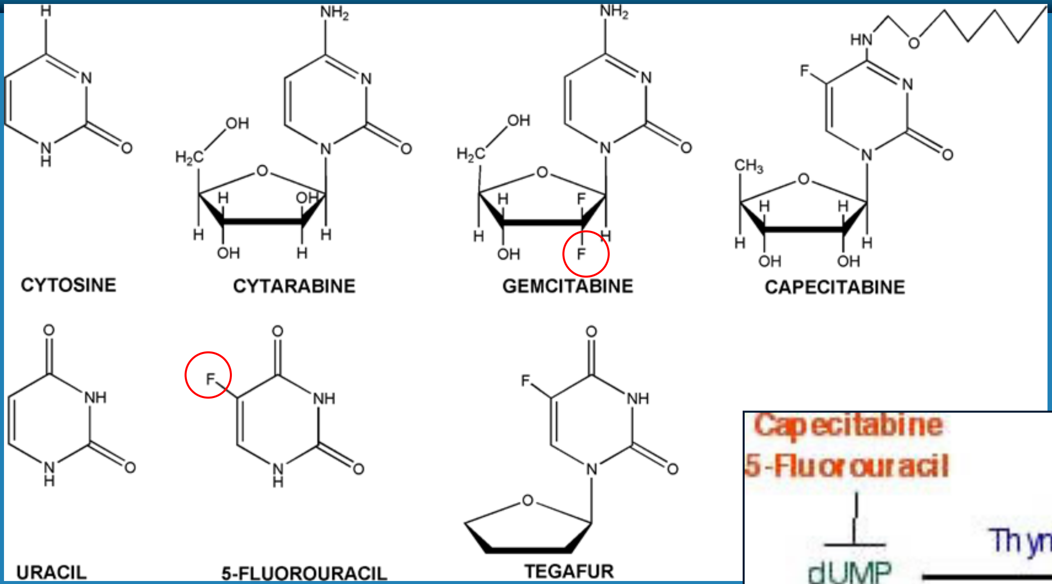
Alkylation

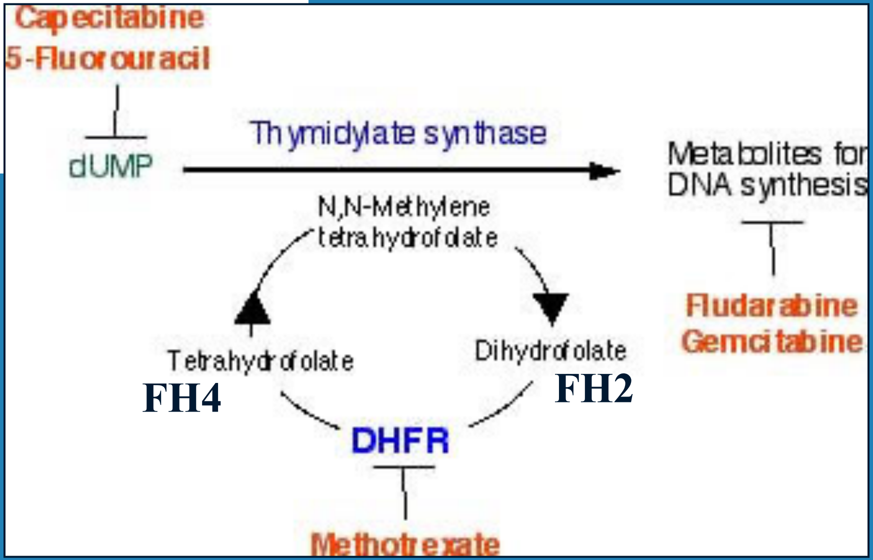


Antimetabolite

- 機制：小分子干擾DNA (RNA)合成
- Adenine: 6-Mercaptopurine, 2-CDA
- Guanine: 6-Thioguanine
- Cytosine: 5-azacytidine, gemcitabine
- Thymidine
  - Methotrexate ┤FH2 reductase→ FH4 → T
  - 5-Fluorouracil →5FdUR ┤T synthetase → T
- DNA polymerase: fludarabine, araC
- RNA reductase: hydroxyurea

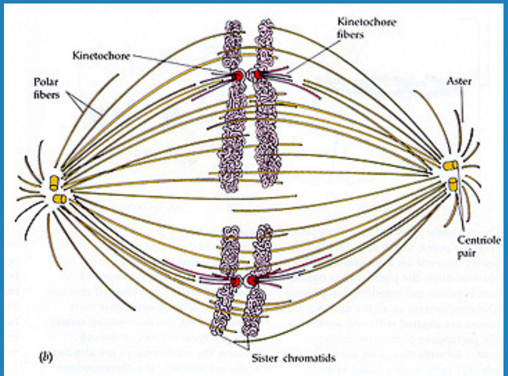
Antimetabolite

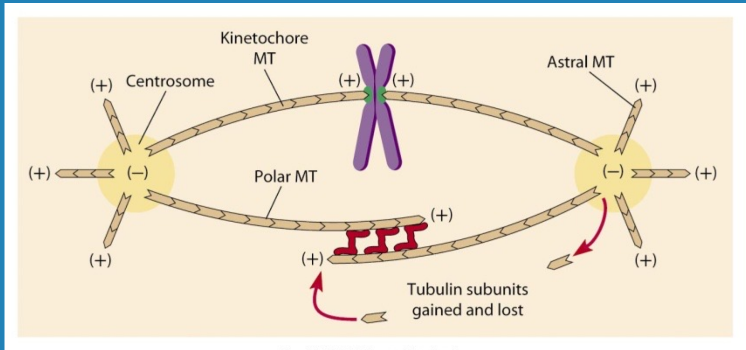




Mitotic Inhibitor

- 機制：阻礙微小管、紡錘體功能
- 分解微小管 (**microtubule**)
  - **Vinca alkaloid (vincristine, vinblastine, vinorelbine)**
- 凍結紡錘體 (**spindle**)、阻礙其分離
  - **Taxane (paclitaxel, docetaxel)**





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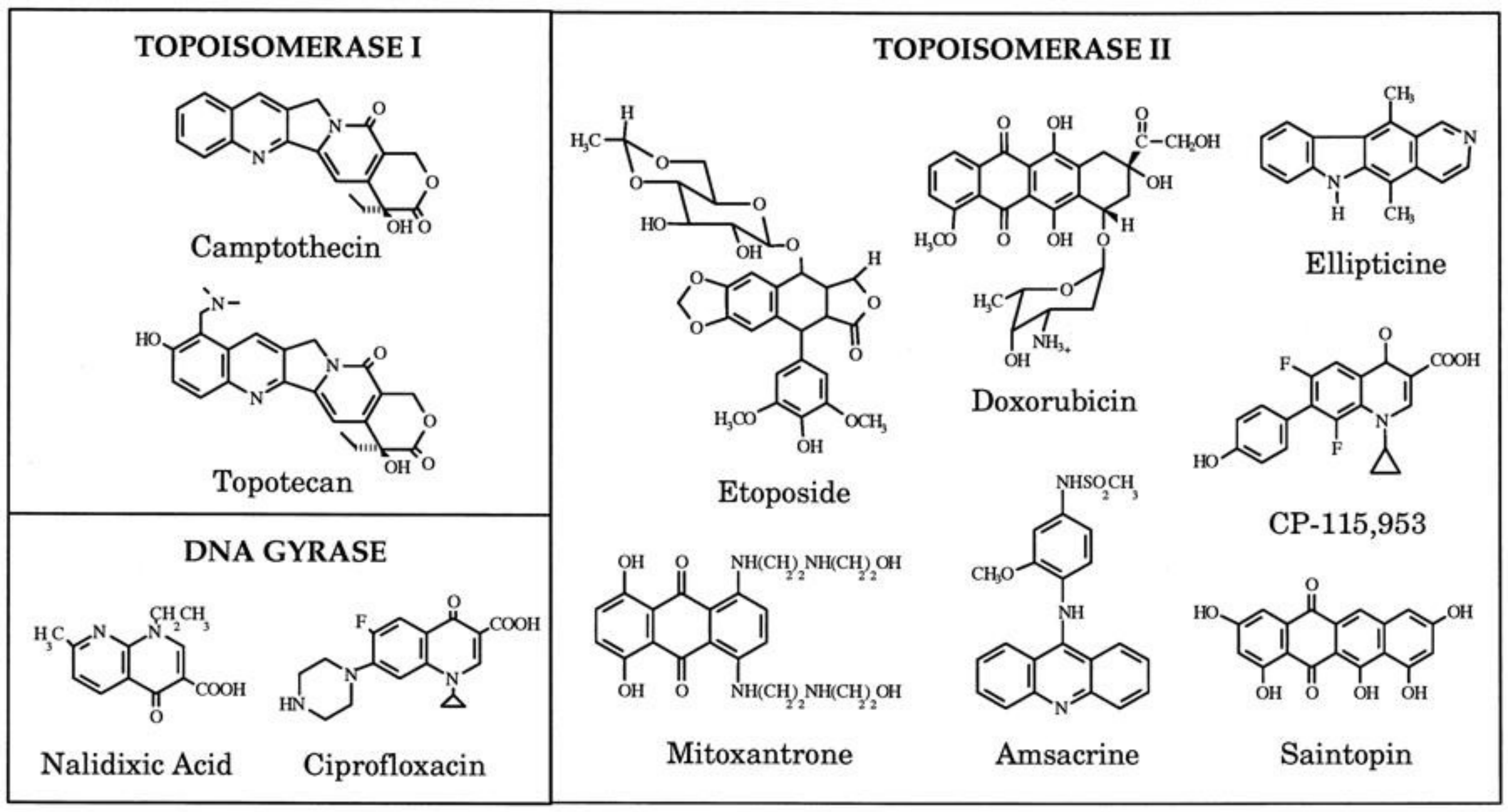
Topoisomerase Inhibitor

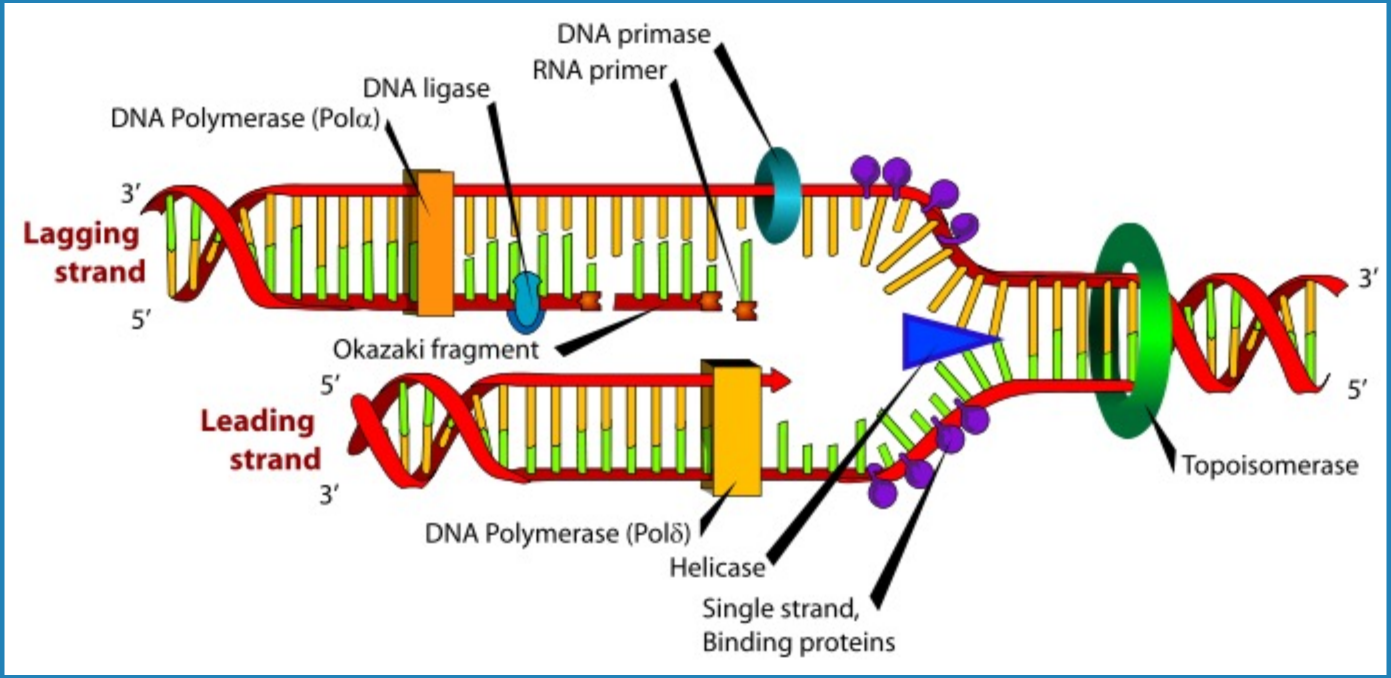


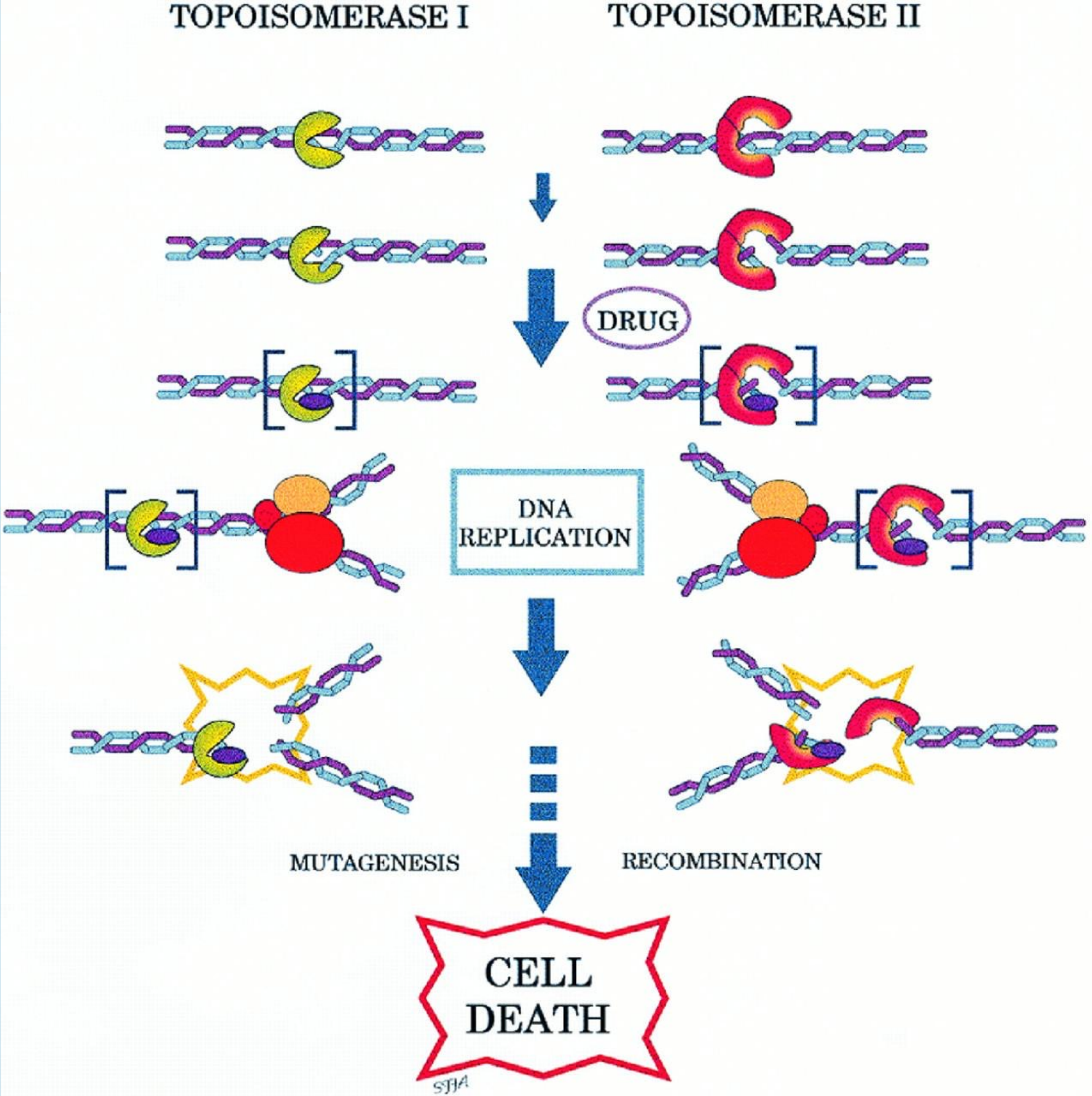
Topoisomerase Inhibitor

- 機制：阻礙 topoisomerase → DNA複製
- Topoisomerase I inhibitor :
  - Camptothecin (irinotecan, topotecan) ┤Topo I → break one strand, uncoil double helix
- Topoisomerase II inhibitor :
  - Epipodophyllotoxin (VP16) ┤Topo II: break two strand, recoil double helix
  - Anthracyclines also inhibit Topo2

Topoisomerase in DNA Replication

- **Break the DNA helix → replication → DNA ligation**




TOPOISOMERASE I
TOPOISOMERASE II
DRUG
DNA REPLICATION
MUTAGENESIS
RECOMBINATION
CELL DEATH
STJA

Antibiotics

- 機制：源於**Streptomyces**，插入**DNA**…
- **Anthracycline (dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone)**
  - **free radical & topo II-dependent DNA injury**
- **Bleomycin ┤DNA ligase; G2-specific**
- **Mithramycin ┤RNA**合成**, osteoclast**

Cancer Chemotherapy

Administration

Plan of Chemotherapy

- Goal of treatment
  - Cure, adjuvant, palliation
  - Risk vs. benefit
- Combined modality therapy
  - Surgery, R/T, C/T, Biotherapy
- Palliative care

Goal of Treatment

分　類　　目　的　　AE　　TRM

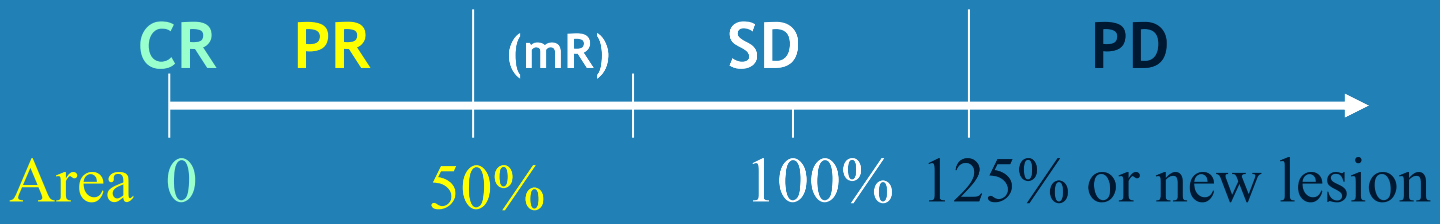
- **Curative**　Cure　Gd 3　< 5-10%
  - AML/ALL, Lymphoma, testis, pediatric ca, high dose chemotherapy
- **Adjuvant**　↓RL　Gd 2　< 2-3%
  - Neoadjuvant: 手術前；提高切除率、保留器官
  - Bladder, colon, sarcoma, head & neck, larynx
- **Palliative**　QoL　Gd 1　< 1%
  - Refractory cancer, breast, pancreas, GI, gynecology, prostate

Monitoring Chemotherapy

- Response
  - Survival time
  - Objective response (RR)
    - T size, tumor marker
  - Subjective changes & QoL
- Adverse Effect (toxicity)
  - Common AE
    - BMS, N/V, mucositis, alopecia
  - Specific AE

Response

- **Survival :**
  - **Overall Survival (OS), Disease-free Survival (DFS), Median Survival.**
- **Objective Response**
  - **RR (CR, PR), SD, PD**



Common Toxicity

- Alopecia
- Nausea/Vomiting
  - alkylator (NitrosU, CDDP, DTIC), A/B
  - Rx: primperan, steroid, serotonin antagonist, aprepitant
- Mucositis → inanition, pain, infection
  - 5FU, MTX, A/B
  - Rx: oral hygiene, A/B gargles, analgesics
- BM suppression
  - infection, bleed, fatigue
  - G-CSF, EPO, transfusion

Specific toxicity (1)

- Anaphylaxis
  - Asparaginase, bleomycin, taxane, Monoclonal Ab > Cisplatin, Doxorubicin
- Cardiomyopathy
  - Anthracycline, herceptin
- Pneumonitis
  - Busulfan, BCNU, bleomycin
- Neuropathy
  - Vinca, Cisplatin, taxol (3h>ci), IFX, HDAC
  - Rx: B12, anticonvulsants, TCA

Specific toxicity (2)

- Pancreatitis
  - asparaginase Rx: NPO
- Nephrotoxicity
  - Cisplatin → Acute renal failure Rx: NS (Cl-)
  - Mitomycin → Hemolytic Uremic Syndrome
- Cystitis
  - Cyclophosphamide, Ifosfamide (10%)
  - Rx: IV fluid, mesna
- Dermatology
  - 5FU, Doxorubicin → Hand-foot syndrome
  - Rx: B6, COX2i

Thanks for your attention.